Ph.D. SYNOPSIS (2019-20)

RESEARCH STUDENT	**GOVANDE ASHVINI VIJAY**
MAIL ID.	ashvinigovande4@gmail.com
MOBILE NO.	**8087531573**
CATEGORY	**Sc**
SUBJECT	**Pharmaceutical Science**
Ph.D. SYNOPSIS TITLE	**"Phytochemical and Pharmacological Evaluation of Novel Herbal Formulations For Anti-Arthritic Activity"**
RESEARCH GUIDE	**DR. S.M. VIJAYENDRA SWAMY**
MAIL ID.	**VIJAYENDRASWAMY@YAHOO.com**
MOBILE NO.	**9586860909**
DESIGNATION	**Principal and Professor**
RESEARCH CENTRE	**S.R.T.M.U Nanded**
UNIVERSITY	**SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED-431606, (MAHARASHTRA STATE), INDIA.**
DATE OF R.A.C.	**29/04/2019**
DATE OF R.R.C.	**22/07/2019**
PLACE OF R.R.C.	**S.R.T.M University, Nanded.**

"Phytochemical and Pharmacological Evaluation of Novel Herbal Formulations For Anti-Arthritic Activity"

A SYNOPSIS SUBMITTED FOR THE REGISTRATION OF *DEGREE OF*

DOCTOR OF PHILOSOPHY

In the Faculty of Pharmaceutical Sciences & Technology

Submitted

By

Miss. ASHVINI VIJAY GOVANDE
M. Pharm.

Under the Guidance of

DR. S.M. VIJAYENDRA SWAMY

(Principal and Professor)

स्वामी रामानंद तीर्थ
मराठवाडा विद्यापीठ,नांदेड.

Swami Ramanand Teerth Marathwada University,

Nanded-431606, (Maharashtra State), India.

(2019-2020)

INDEX

SR.NO.	CONTENT	PAGE NO.
01.	ABSTRACT OF PROPOSED WORK PLAN	04
02.	INTRODUCTION	05-7
03.	REVIEW OF LITERATURE AND DEVELOPMENT IN THE SUBJECT	8-10
04.	OBJECTIVES OF RESEARCH	11
05.	METHODOLOGY TO BE ADOPTED	12-13
06.	IMPORTANCE OF STUDY	14
07	SIGNIFICANCE OF THE STUDY	15
08.	PROPOSED WORK PLAN	16
09.	KEY REFERENCES	17-18

1. Abstract of proposed work plan

Medicinal plants have been a valuable source of natural active phytoconsituents that play an important role in treatment of many human diseases. This is mainly because these herbs/plants are relatively economical, easily available and their uses were decided on ancestral experience. In addition, synthetic drugs are not only expensive and inadequate for the treatment of disease, but are also faced with adulteration and side effects. Therefore, medicinal plants have been useful in the development of new drugs and continue to play valuable role in the drug discovery process.

Arthritis is a chronic, inflammatory, systemic autoimmune disease characterized by pain, swelling and stiffness. About 1% of total world's population are suffering from rheumatoid arthritis, women are most often affected than men. In India about more than 20% of total population is suffering from arthritis. Various allopathic medications have been prescribed to alleviate symptoms of this disease which results into associated side effects like heart attack, stroke, stomach ulcers, bleeding from the digestive tract, and kidney damage etc. Hence the use of herbal medicine is becoming popular due to toxicity and side effects of allopathic medicines. **Therefore, the present study is aimed to evaluate "Phytochemical and Pharmacological evaluation of novel herbal formulations for Anti-arthritic activity"**

Keywords- Rheumatoid Arthritis, medicinal plant.

2. Introduction

Arthritis - It is a Greek word, Arthro –Joint; itis – Inflammation. Quite literally, Arthritis means joint inflammation[(1)]. Rheumatoid arthritis (RA) is most common chronic, inflammatory[(2)], autoimmune and progressive disorder affecting the synovial joints[(3)]. It causes destructive changes in the cartilage and bone[(4)], swelling, long-term (chronic) pain, stiffness[(5)], which leads bony outgrowths restricting mobility of the joint occur in the patients, especially in the morning, difficulty performing daily activities, disability, ultimately affects a person's ability to carry out everyday tasks, restricts the quality of life and causes premature death etc.[(4)]. It is characterized by both local and systemic inflammation with elevated plasma concentration of pro-inflammatory cytokines, such as interleukins-6 (IL-6), interleukin 1b (IL-1b), tumor necrosis factor-alfa (TNF-a), and acute phase proteins[(6)].

It is reported that rheumatoid arthritis occurs in all the ethnic groups all over the world[(1)]. About 1% of total world's population has rheumatoid arthritis[(7)], women are most often affected than men. The prevalence of RA is lowest in Black Africans & Chinese whereas[(1)] in India about more than 20% of total population is suffering from arthritis[(8)]. Prevalence of RA increases with increase in age group with 5% of women & 2% of men over ages of between 40 & 50 years[(1)]. The rheumatoid arthritis also occur in children is known as juvenile idiopathic arthritis and its ratio is 1:1000[(9)].

PATHOPHYSIOLOGY

The bones provide mechanical support and joint gives flexibility, precision of movement, to the body. The movable joint, is consist of synovial membrane, inside membrane synovial fluid is present which lubricates and nourishes articular cartilage, which is necessary for joint movement. Arthritis is an disease which affects synovial fluid of synovial membrane this causes pain and swelling[(10)]. In rheumatoid arthritis the joint mainly affected of wrist, hand, knees, ankles and feet. It typically occur on same joint of body, it can also affect the other organ of the body such as the eyes, skin, heart, lungs, kidneys, nervous system and digestive tract[(11)].

Rheumatoid arthritis is autoimmune disease in which body attacks itself by mistake. It is caused due to genetic (HLA-DR1 & HLA-DR4) and environmental factor[(12)] like smoking, specific pathogen (e.g gut bacteria) causes modification in own antigen[(1)]. Due to the

susceptibility of gene HLA-DR1 & HLA-DR4 the immune cell are confuse to recognize protein itself as antigen. The antigen is get picked up by antigen presenting cell and carried towards lymph node. These antigen presenting cell activates CD4 T Helper cell. The T cell stimulates the proliferation of B cell which differentiates plasma cell to produce specific antibody against self antigen (Anti-IgG antibody/ Rhumatoid factor). In RA T Helper cell and antibodies enter in circulation and rich the joints. Inside the joint T Helper cell secrete cytokines like interferon gamma and interleukins-17 which recruits more inflammatory cell like macrophages into the joint space. Macrophages produces more cytokines like interleukins (IL-6), interleukin 1b (IL-1b), tumor necrosis factor-alfa (TNF-a) which together with T cell cytokines stimulates synovial cell proliferation. The increases in synovial cell in joint space produce pannus which is fibrous tissue around the articular cartilage [(13 &14)]. Due to the adhesion of pannus, the articular cartilage is progressively eroded and destroyed loosing all its smooth texture with further progress of disease, the cartilage gets completely worn off and surface of the bone becomes raw (bony Ankylosis). As a disease progresses multiple joints on both side of the body inflamed and gradually destroyed[(1)].

Rheumatoid arthritis also causes several extra articular problems which includes:

Low grade fever with inflammation of blood vessels (vasculitis), Inflammation of pleural cavity along with pleural effusion, Inflammation of pericardium (pericarditis), Peptic ulcer, hemorrhage and perforation of bowel, Profound fatigue, lethargy and weight loss, Anemia and splenomegaly[(10)].

There is no known complete cure for rheumatoid arthritis but the precautions are to be taken to prevent the re-attack of the disease. Regular physical exercises are advised for the improvement of elasticity of tendons and ligaments which was lost because of arthritis[(1)]. Most of the agents (non biologies) currently in use in the treatment of rheumatoid arthritis have side effects and toxicities that prevent either their long-term use or prevent dosing at levels that might provide superior disease modifying effects[(15)]. Although currently available treatments include non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin[(16)], etoricoxib[(3)], disease modifying anti-rheumatoid drugs (DMARDs) as methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, corticosteroids such as prednisolone, methylprednisolone[(16)], immunosuppressants[(3)] are used in mono or combination therapies[(2)]

to reduce the patient's pain and joint inflammation, minimize loss of function and decrease the progression of joint damage[6]. However, prolonged use of these drugs is associated with deleterious side effects such as gastric ulceration, hemorrhage, anemia, and kidney dysfunction. Because of this reason, many patients are seeking alternative approaches for providing an effective cure for the treatment of disease and to overcome the serious drawbacks such as gastrointestinal bleeding and bone loss[3].Despite considerable progress of arthritis and several limitations of NSAIDs and other drugs, search for newer drugs is necessary. The modern medicine has also started admitting that ayurveda and herbal medicine, has a lot of positive influence on the treatment of various diseases like cancer, memory deficit and Alzheimer, atherosclerosis, diabetes, cardiovascular diseases, ulcer, antioxidant activities, arthritis etc[4].

According to the World Health Organization (WHO), 80% of the population in developed countries relies on traditional medicine[17] for their primary healthcare. Despite considerable progress in therapies using expensive synthetic drugs, the search for herbal remedies is growing which can be accounted for the effectiveness, minimal side effects in clinical experience, and relatively low cost of the herbal drugs[18]. A large number of medicinal plants *Ajuga bracteosa, Alangium salvifolium, Alpinia galangal, Bacopa monniera, Barringtonia racemosa, Cedrus deodar, Cocculus hirsutus, Cyperus rotundus, Vernonia anthelmintica etc.* have been tested and found to contain active chemical constituents like phenols, coumarins, essential oils, monoterpenes, catechins, quinones, carotinoids, flavanoids, alkaloids, anthocyanins and xanthenes which may produce curative properties against arthritis[8].

From the above study it was found that herbal drugs/ medicinal plant or their extracts are prescribed widely, even when their biologically active compounds are unknown. Exploration of the chemical constituents of plants and pharmacological screening would provide the basis for developing new lead molecules in strategic favor of Natural product Drug Discovery[8]. This shows the need of exploration of various medicinal plants for evaluation of rheumatoid arthritis activity. With this background present study was aimed for **"Phytochemical and Pharmacological evaluation of novel herbal formulations for Anti-arthritic activity.**

3. Review of Literature and Development in the subject (Previous work done in the relevant area)

1. Nishat F, Syeda JF, 'Pharmacological Screening for Anti-Arthritic Activity of *Moringa Oleifera'*. 2016; 9 (3): 106-111: In this study of arthritis, the leaf extracts of *Moringa oleifera* (MO) are used against formaldehyde-induced arthritis in laboratory rats. Arthritis was induced in albino Wistar rats by administration of 0.1 ml formaldehyde into subplantar region of the right hind paw. Diclofenac sodium (10 mg/kg, i.p.) was used as the standard drug. Ethanolic leaf extracts of MO at doses of 250 and 500 mg/kg and aqueous leaf extract at 500 mg/kg body weight were administered for 10 days. From result it was found that a aqueous leaf extract 500 mg/kg show significant reduction in paw edema volume, paw thickness, arthritis score, and CRP levels when compared to standard drug.

2. Venu K, Prasenjit M, Manish KT, et.al, 'Antiarthritic potential of aqueous and ethanolic fruit extracts of *"Momordica charantia"* using different screening models'. 2018; 10 (3): 258-264: carried out an anti-arthritic activity on ethanol extract of *Momordica charantia* fruit by using different *in-vivo* model like formaldehyde, Freund's adjuvant-induced arthritis in rats and Collagen induced arthritis model in mice. From the present experimental findings it was observed that both pharmacological and biochemical parameters are reduces at the doses of 200 and 400 mg/kg aqueous extract of *M. charantia* possesses potentially useful anti-arthritic activity

3. Alamgeer, Ambreen MU and Umme HH, 'Anti-arthritic activity of aqueous-methanolic extract and various fractions of *Berberis orthobotrys Bien ex Aitch'*, (2017); 17:371: carried out an anti-arthritic activity of roots and stem bark of *Berberis orthobotrys* by using *in-vitro* model, protein denaturation (bovine serum albumin and egg albumin) and membrane stabilization methods and *in-vivo* model like turpentine oil, formaldehyde and Complete Freund Adjuvant (CFA) models. The results of given study support traditional use of *B. orthobotrys* as potent anti-arthritic agent that may be proposed for rheumatoid arthritis treatment.

4. Alamgeer, Umme HH, Ambreen MU et.al, 'Evaluation of *in-vitro* and *in-vivo* anti-arthritic potential of *Berberis calliobotrys'*. 2015; 10: 807-819: In this study the anti-arthritic effect was evaluated by using 70% methanol extract and *n*-butanol and aqueous fractions of *Berberis calliobotrys* using both *in vitro* and *in vivo* arthritis models. Extract and

fractions were investigated *in vitro* for inhibition of protein (bovine serum and egg albumin) denaturation and human red blood cell membrane stabilization. *In vivo* antiarthritic activity of extract and fractions at 50, 100 and 200 mg/kg was assessed using turpentine oil and formaldehyde-induced arthritis, while, 200 mg/ kg dose was evaluated against complete Freund's adjuvant-induced arthritis. *B. calliobotrys* produced significant dose dependent inhibition of protein denaturation and human red blood cell membrane stabilization. In turpentine oil, formaldehyde and complete Freund's adjuvant-induced arthritis models, *B. calliobotrys* significantly reduced joint and paw swelling.

5. Bendele AM, 'Animal models of rheumatoid arthritis'. 2001; 1(4):377-385: This study evaluate anti-arthritic potential of synthetic drugs corticosteroids, methotrexate, nonsteroidal anti-inflammatory drugs, cyclosporin A, leflunomide interleukin-1 receptor antagonist (IL-1ra) and soluble TNF receptors by using different animal model, adjuvant arthritis, rat type II collagen arthritis, mouse type II collagen arthritis and antigen induced arthritis. From the above study it was found that these drugs are used in the clinical treatment of RA but only at low doses because of the toxicities associated with chronic use.

6. Kore KJ, Shete RV, Desai NV, 'Anti-Arthritic activity of Hydroalcoholic extract of *Lawsonia Innermis'*. 2011; 3 (4): 217-224: In this study, anti-arthritic activity of hydroalcoholic extract of *Lawsonia innermis* is done by freund's adjuvant induced arthritis model and formaldehyde induced arthritis model. Paw edema, paw diameter and loss in body weight during arthritis condition was corrected on treatment with hydroalcoholic extract of *Lawsonia innermis* after comparison with Diclofenac (standard drug). The observed anti-arthritic activity may be due to the presence of phytoconstituents such as alkaloid and flavonoids.

7. Himanshu S, Prerna C, Surender Singh, 'Evaluation of the anti-arthritic activity of *Cinnamomum cassia* bark extraction experimental models'. 2018; 7: 366-373: carried out an anti-arthritic activity of hydroalcoholic extract of *Cinnamomum cassia* bark using formaldehyde-induced arthritis and complete freund's adjuvant (CFA)-induced arthritis. The rats were divided into six groups as follows: normal control, disease control, indomethacin group (3 mg/kg, p.o.) and three groups, treated with 50, 100 and 200 mg/kg CCHE. CCHE treatment significantly reduced joint swelling as well as IL-1 and TNF-levels in a dose dependent manner.

8. Manjusha C, Vipin K, Pankaj KG et.al, 'Anti-arthritic activity of *Barleria prionitis Linn*. Leaves in acute and chronic models in Sprague Dawley rats'. 2014; 52: 199–209: The present investigation was designed to evaluate anti-arthritic potential of ethyl acetate and chloroform extract from leaves of *Barleria prionitis*. This fraction was evaluated at two doses 125 and 250 mg/kg by using different model formaldehyde-induced acute non immunological and freund's complete adjuvant-induced chronic immunological arthritis in rats. In the present investigation, dose dependent and significant inhibition of edema and protects synovial membrane and exhibits promising anti-arthritic activity.

9. Vikrant A, Vivek KG, Ranjeet K, 'A Review on Plants having Anti-Arthritic Potential'. 2011; 7 (2): 131-136: This study is carried out to evaluate anti-arthritic potential of herbal plant because allopathic medications associated with side effects like gastrointestinal bleeding and bone loss (osteoporosis). This study involves various plant drugs along with their chemical constituents and pharmacological profile which focus on the dose administered, bioactive extract involved in anti-arthritic mechanism.

10. Mohannad Mobarak OB, Ghofran Noor MQ, Abdulmohsen SA, et.al, 'Rheumatoid Arthritis, Pathophysiology and Management'. 2018; 70 (11): 1898-1903: In this study the pathophysiology, clinical picture, and management of rheumatoid arthritis, which focus on the newer modalities. Rheumatoid arthritis is considered one of the most common, and particularly attacks the joint and causes articular as well as extra articular manifestation. Various treatments for rheumatoid arthritis are available which significantly decreasing long-term auricular and extra auricular complications. Combining DMARDs (disease-modifying anti-rheumatic drug) with corticosteroids will result in significantly better outcomes than monotherapy with any DMARD, and decrease long term morbidity associated with this condition.

11. Refaz AD, Mohd S, Parvaiz HQ, 'General overview of medicinal plants': A review. 2017; 6(6): 349-351: Medicinal plants are regarded as rich resources of traditional medicines and from these plants many of the modern medicines are produced. For thousands of years medicinal plants have been used to treat health disorders, to add flavor and conserve food and to prevent diseases epidemics. The secondary metabolites produced by the plants are usually responsible for the biological characteristics of plant species used throughout the world.

4. Objectives of Research/ Proposed Hypothesis

Need of Study:

Rheumatoid arthritis is very common disease and various synthetic drug are available for the treatment of rheumatoid arthritis but they have some side effect. Therefore number of medicinal plants are screened for arthritic potential but not fully explored. So, the study will be conducted on those medicinal plants which are not fully studied for anti-arthritic activity.

Aim and objectives of Research Topics:

Aim: "Phytochemical and Pharmacological evaluation of novel herbal formulations for Anti-arthritic activity"

Objectives:

- Phytochmical investigation and standardization of selected plant extracts.
- *In-vitro* antioxidant activity of extracts.
- Acute oral toxicity study of selected plant extract.
- To prepare various formulation of plant extracts for checking anti-arthritis potential.
- To evaluate *in-vivo* pharmacological screening techniques for anti-arthritis activity.
- To screen anti-arthritis potential of various herbal plant extracts.

5. Methodology to be adopted

The methodology of research work will be selected on the basis of literature survey as follows:

1. **Collection, Identification and Authentication of plant material:** The whole plant or its parts of selected plant will be collected from known sources. The sample will get identify and authenticate by the botanist of region.

2. **Pharmacognostic evaluation of plant material:** The whole plant or its parts will be subjected to pharmacognostic evaluation i.e for morphological and microscopic evaluation and powder characteristic.

3. **Processing of plant material:** The collected plant material will be subjected to processing such as drying, grinding, sieving etc. as per official standard.

4. **Extraction of plant material:** Extraction of plant material will be carried out by selecting specific solvent system and extraction method on the basis of literature survey.

5. **Phytochemical screening of plant material:** Phytochemical screening plant material will be carried out for analyzing:

    1) Extractive value
    2) ash content
    3) Acid and water soluble ash
    4) Loss on drying

6. **Phytochemical qualitative analysis of plant extract:**
    - Phytochemical qualitative analysis of selected plant extract will be carried out by preliminary phytochemical test i.e presence of Carbohydrates, Tannin, Alkaloids, Glycosides, Flavonoides, Steroids, Amino acid and proteins etc.
    - TLC fingerprinting of extract
7. **Phytochemical quantitative analysis of extract:** The total phenolic & flavonoid content will be determined by phytochemical quantitative analysis.

8. **Pharmacological screening of plant extracts for:**
    - Acute oral toxicity study will be carried out for plant extract as per official guidelines like OECD.
    - Pharmacological screening for Anti-oxidant activity of plant extracts will be carried out.
    - Preparation of Formulation of plant extract
    - Pharmacological screening for anti-arthritic activity by animal model as per reference standard methods.
9. **Interpretation of data and its presentation.**

6. Importance of study

Plants are one of the most important sources of medicines, India is known as the "Emporium of Medicinal plants" due to availability of several thousands of medicinal plants in the different bioclimatic zones[7]. Natural products from plants have played a remarkable role to cure a different diseases from ancient times and are highly effective preventive medicine when compared to expensive synthetic drugs. It have been useful in the development of new drugs and continue to play a valuable role in the drug discovery process. Herbal medicines have already formed the basis of therapeutic use in developing countries, but recently have also seen an increase in the use of herbal medications in the developed world as well. This is mainly because these herbs/plants are relatively cheap, easily available and their uses are dependent on ancestral experience. A study conducted by World Health Organization (WHO) has reported that about 80% of world's population relies on traditional medicine[17].

Rheumatic diseases are considered public health problems affecting millions of people worldwide resulting in high and rising health-care costs. In 2003, the United States of America spent a total of 128 billion US$ on rheumatoid arthritis (RA), 3.6 billion US$ were spent on drug therapies. In the period from 2007 to 2009, US statistical data indicate an increase of approximately a million of new RA cases per year. Rheumatoid arthritis affects approximately 0.5-1% of the world population being more common in women than in men, and in ages between 40 and 50 years [19].

Keeping this in view, now many researchers switching theirs field from synthetic to natural side in order to explore nature more and more. Synthetic drugs not only cure disease but also causes severe side effect to human body.

7. Significance of the study (Research Outcomes)

- The study will be supportive to treat the various joint problem.
- Plant based medicine is expected to have fewer side effects as compared to the modern drugs.
- The present study will be helpful to minimize the cost of the treatment of anti-arthritic drug.
- This study uses the plants as medicines which have been not fully explored and that's why it will be very important to investigate the anti-arthritic potential of these plants.
- The aim of this study is to isolate the potent component from plants which have maximum anti-arthritic effect.

8. Proposed work Plan/ Formulation and Structure of Study
Year-wise Plan of work and targets to be achieved

First Year:
Literature survey, collection of plant material, pharmacognostic evaluation of plant material i.e for morphological and microscopic evaluation and powder characteristic of selected plant, collected plant material will be subjected to processing such as drying, grinding, sieving, phytochemical screening of plant material will be carried out.

Second year:
Extraction of plant material will be carried out by selecting specific solvent system and extraction method on the basis of literature survey, phytochemical qualitative and quantitative analysis for separation and isolation of compound of selected plant extract. *In vitro* pharmacological screening for anti-oxidant activity of different plant extracts will be carried out.

Third year:
Acute oral toxicity study will be carried out for plant extract as per official guidelines, Preparation of formulation of plant extract, pharmacological screening for anti-arthritic activity by animal model as per reference standard methods, interpretation of data and its presentation.

9. Key References

1) Mohana LS, Vatsalya C, Ashok CK, Kumar SD, A Review on Rheumatoid Arthritis-its Complications and Herbal Treatment, Journal of Global Trends in Pharmaceutical Sciences, 2013; 4 (4): pp.1310-1317.

2) Alamgeer, Umme HH, Ambreen MU, Shahid R, Evaluation of *in-vitro* and *in-vivo* Anti-Arthritic potential of *Berberis calliobotrys*, Journal of the Bangladesh Pharmacol, 2015; 10: pp 807-819.

3) Nishat F, Syeda JF, Pharmacological Screening for anti-arthritic Activity of *Moringa Oleifera*, Asian Journal of Pharmaceutical and Clinical Research, 2016; 9 (3): pp 106-111.

4) Manjusha C, Vipin K, Pankaj KG et.al, Anti-arthritic activity of *Barleria prionitis Linn*. Leaves in acute and chronic models in Sprague Dawley rats, Bulletin of Faculty of Pharmacy, Cairo University, 2014; 52: pp 199-209.

5) Alamgeer, Ambreen MU, Umme HH, Anti-arthritic activity of aqueous-methanolic extract and various fractions of *Berberis orthobotrys Bien ex Aitch*, BMC Complementary and Alternative Medicine, 2017; 17 (371): pp 1-16.

6) Vikrant A, Vivek KG, Ranjeet K, A Review on Plants having anti-Arthritic Potential, International Journal of Pharmaceutical Sciences Review and Research, 2011; 7 (2): pp 131-136.

7) Kore KJ, Shete RV, Desai NV, Anti-Arthritic activity of Hydroalcoholic extract of *Lawsonia Innermis,* International Journal of Drug Development & Research, 2011; 3 (4): pp 217-224.

8) Vivek KB, Irchhaiya R, Shashi A, Antiarthritic Activity of Some Indigenous Plants: A Review, International Journal of Pharmaceutical Sciences and Research, 2019, pp1-5.

9) Venu K, Prasenjit M, Manish KT, Sumanta M, Nimma VR, Antiarthritic Potential of Aqueous and Ethanolic Fruit Extracts of *"Momordica charantia"* Using Different Screening Models. Pharmacognosy Research, 2018; 10 (3): pp : 258-264.

10) Dr. Bodhankar SL, Dr. Vyawahare NS, A Textbook of Pathophysiology, Nirali Prakashan, 10th edition, 2016: pp 12.3-12.10.

11) Dr. Kaushik M, A Textbook of Pathophysiology, Pee Vee, 2018: pp 325-328.

12) Mohannad Mobarak OB, Ghofran Noor MQ, Abdulmohsen SA, et.al, Rheumatoid Arthritis, Pathophysiology and Management, The Egyptian Journal of Hospital Medicine, 2018; 70 (11): pp 1898-1903.

13) Harsh Mohan, Textbook of Pathology, Jaypee Brothers Medical Publishers LTD, 6th edition, 2010: pp 851-853.

14) Rang HP, Ritter JM, Flower RJ, Handerson G, Rang and Dale's Pharmacology, Elsevier Churchill Livingstone, 8th edition, 2016: pp 325-328.

15) Bendele AM, Animal models of rheumatoid arthritis, Journal of Musculoskel Neuron Interact 2001; 1(4): pp 377-385.

16) Himanshu S, Prerna C, Surender S, Evaluation of the anti-arthritic activity of *Cinnamomum cassia* bark extract in experimental models, Integrative Medicine Research, 2018; 7: pp 366–373.

17) Abdullah AN, Rownak J and Mohammed R, *Zingiber officinale*: A Potential Plant against Rheumatoid Arthritis, Hindawi Publishing Corporation, 2014; pp 1-8.

18) Ali K, Maedeh M, Mahmoud RK, Herbal versus synthetic drugs; beliefs and facts, Journal Nephropharmacology, 2015; 4 (1): pp 27–30.

19) Carolina da SC, Luiz Eduardo CA, Silene PK, et.al, Study of advanced rheumatoid arthritis, Brazilian Journal of Biomedical Engineering, 2014; 30 (1): pp 54-63.

Name of Research Candidate **Signature**	Ms. Ashvini Vijay Govande
Remarks of The Guide	
Name & Designation of Research Supervisor **Signature**	Dr. Vijayendra Swamy S.M.; Principal and Professor, Channabasweshwar Pharmacy College (Degree), Latur.